NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases

DIABETES MELLITUS

Between 10 and 11 million Americans, about 1 in 20, have diabetes mellitus, often simply called diabetes. This chronic disease interferes with the body's ability to derive energy from glucose, a type of sugar that is an important product of digested food.

When diabetes strikes children, it is in a form that requires daily injections of the hormone insulin. Most people with diabetes have another form of the disease that begins in adulthood and that can escape notice by the person affected for many years.

While the onset of childhood, or insulin-dependent, diabetes can be much more dramatic than that of an adult or noninsulin-dependent diabetes, both afflictions are life-threatening. Both are associated with complications that can develop even while the underlying diabetic condition causing them is being treated. The complications--among them, eye, kidney, heart, and nerve disease--can be serious and, for most diabetic patients, are the disease's greatest threat.

The understanding that diabetes has more than one cause--and that different forms of diabetes result in the same long-term complications--is a product of research conducted in the years following the first great diabetes breakthrough, the discovery of insulin in 1920. Based on this new understanding of diabetes, more recent research has focused on insulin-dependent diabetes (IDDM) and noninsulin-dependent diabetes (NIDDM) as conditions that must be approached individually in both research and therapy in different ways.

This research has led to such major developments as new purified forms of insulin, synthetic human insulin made by recombinant DNA techniques, blood glucose monitoring technology, and insulin pumps, all important options for people with IDDM. While these technologies can also be applied in NIDDM, this disorder is now recognized as one that can, in the majority of cases, be treated and often prevented through diet and exercise.

Even with these advances, there is as yet no cure for diabetes, and the complications of this disease remain a threat:

- People with diabetes are about twice as likely as those without diabetes to have heart disease.

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- Strokes occur two to six times more frequently in people with diabetes than in those without the disease.

- After 15 years of diabetes, about one-third of persons with IDDM and one-fifth of people with NIDDM have signs of kidney disease. Diabetes accounts for a quarter of all new cases of end-stage renal (kidney) disease.

- Diabetes is the leading cause of blindness in middle-age Americans.

- Perinatal mortality--death of an infant occurring any time from about the 20th week of pregnancy to several weeks after birth--is two to four times higher in pregnancies in which the mother is diabetic than in pregnancies uncomplicated by diabetes. Five to 10 percent of infants of women who are diabetic before they become pregnant have congenital malformations at birth.

While the complications of diabetes can be a serious threat to health, research is providing information that can be used to minimize the risk and the disability from these conditions. For example:

- Through research, scientists have determined that careful control of blood glucose levels in a pregnant diabetic woman can reduce the risk of perinatal mortality to that seen in women without diabetes. Preliminary studies have shown that by controlling diabetes before the woman becomes pregnant, it may now be possible to eliminate the increased risk of congenital malformation in infants of diabetic mothers.

- Application of techniques now available for preventing and caring for sores and infections in the legs and feet of people with diabetes could reduce by an estimated 50 percent the number of amputations necessary as a result of diabetes.

- Improved treatments for diabetic eye disease can greatly reduce the incidence of blindness associated with diabetes. Through research on eye complications, scientists have developed drug treatments now being tested for their potential in preventing eye disease and other complications of diabetes.

- Research has laid the groundwork for a major clinical trial now under way to test whether very careful diabetes control can prevent or limit diabetic complications.

Even more hopeful than these advances, however, is the increasing ability of scientists to use new research techniques to probe the mechanisms that underlie normal metabolism and the defects that cause diabetes. This year, scientists were able to clone the gene for the insulin receptor. Insulin-producing

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cells (islet cells) of the pancreas were extracted and purified using new techniques and transplanted into human patients for the first time. New synthetic techniques were used to produce a chemical facsimile of glucagon, a hormone that, like insulin, regulates glucose metabolism. All these advances were made possible by new technologies developed in the course of basic research. In time, discoveries made possible by these technologies may lead to solutions to diabetes as a public health problem.

The Causes of Diabetes

Insulin is a hormone made by the pancreas, a gland located just below the stomach. Insulin is essential for the normal metabolism of glucose. If there is insufficient insulin, or if insulin for some reason does not act effectively, blood glucose rises. Diabetes treatment is aimed at lowering elevated blood glucose levels.

Insulin-Dependent Diabetes Mellitus and the Immune System

People with insulin-dependent diabetes make no insulin and therefore must have injections of the hormone each day to survive. An increasing amount of evidence supports the theory that the pancreas' ability to secrete insulin is lost in IDDM as a result of the destruction of insulin-secreting cells by the patient's own immune, or disease-fighting, system (a so-called autoimmune process). Among the evidence are findings of altered activity of white blood cells, which normally play important roles in immune responses.

A strain of rats developed at the University of Massachusetts at Worcester has provided an important resource for research on IDDM. These rats have a genetic predisposition to developing a form of IDDM. Last year, Dr. Aldo Rossini and colleagues at the university showed that transfusions of whole blood from healthy rats to diabetes-prone animals could prevent the onset of diabetes. This year, the group showed that certain types of white blood cells transfused from healthy to diabetes-prone rats had the same effect, demonstrating that the white blood cells were responsible for protection from the disease.

In a complementary line of research in human patients, Drs. Richard Spielman, Franz Matschinksy, and colleagues at the University of Pennsylvania, Philadelphia, compared the production of a substance called interleukin-2 (IL-2) by white blood cells in 26 people with IDDM, 6 people with NIDDM and 40 nondiabetic volunteers. White blood cells release IL-2 when they are sensitized or "aroused" by the presence of a foreign substance. The researchers found that white blood cells (WBC's) in the IDDM patients produced less IL-2 than WBC's in either of the other two groups. The decreased IL-2 production

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may impair the defensive response to a viral infection of the insulin-producing islet cells in the pancreas, or may create an imbalance in the immune system that could make the cells vulnerable to harm from autoimmune destruction.

The studies on the diabetes prone rats and on human immunologic responses are providing a clearer picture of how the immune system is involved in IDDM and how the disease might one day be prevented. Both are examples of research conducted at National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK)-supported Diabetes-Endocrinology Research Centers (DERC's). DERC's and Diabetes Research and Training Centers (DRTC's) receive support to establish "core" research facilities, each with specialized research capabilities. Scientists can draw on each core's expertise rather than duplicating equipment and training. The core concept is important in an era of increasing scientific specialization.

Noninsulin-Dependent Diabetes Mellitus and the Insulin Receptor

In the University of Pennsylvania studies just described, the white cell responses of NIDDM patients were the same as in volunteers without diabetes. This finding reflects the fact that NIDDM and IDDM do not have the same underlying cause. While there is probably a defect in the function of insulin-producing cells in NIDDM, the pancreas retains an ability to secrete the hormone in this disease. As a result, scientists are having to look beyond the pancreas for the cause of NIDDM.

The explanation for NIDDM lies at least partially in the tissues on which insulin acts. Cells of the target organs of insulin have surface receptors for the hormone. To act on the cell, insulin must bind with these receptors, and the hormone-receptor binding sets off a series of steps, as yet incompletely understood, which result in the processing of glucose by the cell.

Defects in insulin receptors or in the steps that follow binding of insulin to the receptor are thought to be part of the cause of NIDDM. Such defects would reduce the effectiveness of insulin even when the person affected produced normal amounts of the hormone, a condition called insulin resistance. Insulin resistance is a hallmark of NIDDM and contributes to elevated blood glucose.

A major step forward this year in research on insulin action was the determination of the structure of the insulin receptor and the gene that determines this structure. Two groups of researchers, among them NIADDK grantees at Memorial Sloan-Kettering Cancer Center, New York; the University of California, San Francisco; Mt. Zion Hospital and Medical Center, San Francisco; and Stanford University, Stanford, California, reported making this advance using slightly

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different techniques. With this information, scientists can test concepts of how the receptor is synthesized, how it is oriented on the cell surface, how it interacts with insulin, and how it acts on intracellular machinery to influence the use of glucose by the cell.

The availability of the insulin receptor presents new opportunities for NIADDK scientists who have been studying it. Two years ago, NIADDK intramural scientists reported that when insulin binds to its receptor, the insulin-receptor unit responds by incorporating phosphate from the cell at a specific site in the insulin receptor. The incorporation of phosphate--or phosphorylation--is known to be a regulatory step, sort of a biochemical "switch," in living systems. These and other researchers subsequently studied this process in people with syndromes of extreme insulin resistance. Some scientists have reported that the phosphorylation step is altered in these conditions.

To further understand the role of phosphorylation in metabolism, scientists have been studying other growth-regulating proteins that, like the insulin receptor, are capable of phosphorylating proteins. One class of these proteins includes the receptor for epidermal growth factor (EGF). Another class consists of the products of oncogenes, or cancer-causing genes found in viruses. Recently, NIADDK intramural scientists Drs. Jesse Roth, Simeon Taylor, and colleagues reported that they had used immunologic techniques to show that the EGF receptor shared much of the structure of the protein product of a viral oncogene. Like the EGF receptor, the viral protein promotes growth and can phosphorylate other proteins. This research showed that these shared functions are apparently reflected in shared structure. However, the viral protein lacks a control sequence present on the EGF receptor. It appears that viruses can take over genes coding for growth-promoting proteins that occur normally in cells. The discovery of these similarities between growth-promoting proteins in viruses and cells was a surprise. Study of these interrelationships can provide insight on the mechanism of how these substances stimulate growth, and how the processes they control can go awry.

Clinical research on the mechanisms of insulin action and resistance is under way at NIADDK's Phoenix Clinical Research Center in Arizona. The Pima Indians of this area have the highest documented incidence of NIDDM of any population group in the world. For 20 years the Pimas have cooperated with the scientific community in Phoenix. This research has led to important insights into NIDDM.

One important goal for the scientists at Phoenix is to characterize exactly how NIDDM develops and what is involved in causing the very high levels of blood glucose seen in some people with this disease. Studies done in Phoenix suggest that

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the process is not a simple one. Dr. Clifton Bogardus and colleagues have described a sequence of events in which insulin resistance is an early defect. There may be a number of causes for insulin resistance. Some evidence supports the theory that insulin resistance can be compounded by an inability of the pancreas to respond appropriately to rising glucose levels. The body, unable to use glucose adequately, turns to fats for energy and the liver begins producing more glucose, exacerbating already elevated glucose levels.

Each of the steps described above may provide a point at which intervention might be aimed to help control high blood glucose in NIDDM. This research contributes to an understanding of the disease, but is also essential to developing new treatments and understanding how currently available treatments can be used to their best advantage.

Diabetes Treatment

The news that generated the most excitement in the diabetes community this year was the announcement by Drs. Paul Lacy and David Scharp at Washington University, St. Louis, Missouri, of the resumption of attempts at transplantation of insulin-producing (islet) cells into human patients. Transplantation, if successful, offers important benefits to insulin-dependent diabetic patients. Transplanted tissue would respond to the moment-to-moment fluctuations in blood glucose level in a way that periodic injections cannot. If complications prove to result from fluctuations--even minor ones--in blood glucose, transplantation could help prevent such complications while at the same time improving glucose control. In addition, transplantation would free diabetic patients from the need for daily injections.

Drs. Lacy and Scharp reported in June results with six patients who received the insulin-producing islet cells. The transplanted cells produced insulin in three of the six patients for up to 8 weeks. The scientists are optimistic that continued studies will lead to a higher success rate and longer function of transplanted cells. In addition, research is aimed at making it possible to transplant insulin-producing cells without the need for drugs to suppress rejection. This work, and much of the basic research that led up to it, was based at the NIADDK-supported DRTC at Washington University.

While insulin-dependent and noninsulin-dependent diabetes appear similar in many ways, insulin administration is optional rather than a necessity for many people with NIDDM. Recent research, however, indicates that in NIDDM patients careful insulin administration not only lowers glucose levels but also, over time, improves how body tissues respond to glucose. Grantee Dr. Orville Kolterman and colleagues at the University of California at San Diego used insulin pumps to maintain glucose levels close to normal over 3 weeks in a group of 14

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patients with NIDDM. After this intense insulin therapy, body tissues were better able to metabolize glucose, the pancreas' ability to secrete insulin was improved, and glucose output in the liver was reduced to normal. These effects persisted even after the treatment ended. This research shows that high glucose levels that result from NIDDM may also increase the metabolic abnormalities in this disease. Because some of these abnormalities apparently can be reversed by bringing blood glucose back to normal with administered insulin, the work opens up an avenue of investigation for potential therapeutic applications of this treatment.

Technology and the Future

Technological advances in the field of diabetes have furnished new devices and techniques for diabetes therapy and have greatly increased the variety and capabilities of research methods available to scientists in this field.

New therapeutic capabilities are enabling scientists to assess the relationship between careful blood glucose control and the development of complications of diabetes. This relationship poses the major current question in diabetes treatment. This year, NIADDK's Diabetes Control and Complications Trial, a clinical trial designed to answer this question, successfully completed its feasibility stage. The study organizers expect to follow the volunteers enrolled until 1993. The outcome of this study will have widespread implications for the treatment of diabetes and the outlook for reducing the long-term illness and disability this disease can cause.

New techniques in molecular biology are allowing scientists to characterize the immunologic changes that lead to IDDM and to identify genetic markers that indicate an increased susceptibility to this disease. This year grantees Drs. Sathyanarayana Srikanta, George Eisenbarth, and their colleagues at the Joslin Diabetes Center, Boston, reported on a study in which they are screening first-degree relatives of IDDM patients for antibodies to insulin-producing cells. These antibodies are found in IDDM patients and are a sign of immunologic activity against these cells. Out of 1,723 nondiabetic relatives of diabetic patients screened, the researchers found 16 relatives with antibodies. One of these 16 subsequently became diabetic, and 6 had abnormally low production of insulin in response to glucose. One initially nondiabetic relative who did not have antibodies also developed diabetes. This type of screening, only now possible because of techniques for detecting antibodies, may have potential for early identification of people at risk for diabetes.

Human insulin made by recombinant DNA techniques has been available for patients with diabetes since 1982. The ability to synthesize hormones has therapeutic usefulness, but it also makes possible structural and functional studies of hormones.

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Last year, Dr. Robert Merrifield of New York's Rockefeller University won the Nobel Prize in chemistry for developing a method to synthesize peptides, short versions of proteins. NIADDK has supported Dr. Merrifield's research for 30 years. This year Dr. Merrifield used this technique to produce purified glucagon, a hormone that has the opposite effect on glucose metabolism that insulin does. His technique enables scientists to construct glucagon molecules with structural alterations and to study how these alterations affect the function of the hormone. This technique will help us understand the function of glucagon and can provide a basis for designing new drugs that could help regulate glucose metabolism.

To fully exploit these new technological capabilities, modern facilities and expert personnel are essential. NIADDK supports seven DRTC's and five DERC's. In addition to specialized core research facilities, the DRTC's have a training component aimed at health professionals.

Diabetes research in recent decades has led to new and effective means to control this disease and help prevent and treat its complications. There is a demonstrated gap, however, between the progress that has been made in research, and the transfer of this knowledge to primary health care practitioners who treat most patients with diabetes. Through both research on the medical care of diabetic patients and professional education, the DRTC's have developed curricula and supportive materials such as computer programs as resources for the instruction of health professionals in the state-of-the-art care of diabetic patients. The DRTC's have cooperated with local medical centers and health departments to make these resources readily available to the community. Thus, in addition to providing the technological base for advanced research on diabetes, the DRTC's are developing through research rapid and effective means by which new scientific information can be passed on to health professionals who can use this expertise to reduce the illness and disability associated with diabetes.

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National Cancer Institute

Cancer of the pancreas, diagnosed in 25,000 Americans annually, is rarely detected until it is in an advanced stage. Although comprising only about 2 percent of all new cancer cases, the disease accounts for about 5 percent of all cancer deaths. It is the fourth most common cause of cancer deaths in men and the fifth most common cause of cancer deaths in women.

Some studies have linked diabetes mellitus with pancreatic cancer, but whether common factors lead to both cancer and diabetes-like changes or if diabetes makes individuals prone to cancer is not known.

At the University of Nebraska Medical Center in Omaha, National Cancer Institute (NCI) grantee Dr. Parviz Pour is studying diabetes as a possible predisposing factor in pancreatic cancer development. Scientists have found that the chemicals alloxan and streptozotocin can induce in hamsters pancreatic cancer that resembles the human disease. In this experimental system, the cancer occurs in cells called ductular stem cells, which in normal hamsters develop into the very specialized cells of the pancreas.

In human adults that develop diabetes, the pancreas produces abnormally large amounts of ductular stem cells. Scientists have suggested that this increased cell growth might be associated with an increased risk of ductular cell cancer. In the animal model, a similar production of large numbers of ductular cells occurs, but this can be suppressed by insulin treatment. The Omaha scientists are also using animal models to study whether insulin will inhibit the development of pancreatic cancer. If successful, the results of these experiments will suggest new approaches for preventing pancreatic cancer in adult diabetics.

At the Stanford University School of Medicine, NCI and National Institute of Allergy and Infectious Diseases (NIAID) grantees Drs. Nelson N. H. Teng and Henry S. Kaplan (now deceased) and coworkers have made monoclonal antibodies that neutralize endotoxins, a family of powerful toxins produced by gram-negative bacteria. Endotoxins are found on the surface of certain bacteria such as Escherichia coli, an organism that lives in the human digestive tract. In healthy people, these bacteria are generally harmless because they are kept under control by the body's immune system.

But surgery and other diseases, including diabetes, can predispose a patient to bloodstream-borne infections called bacteremia, and the endotoxins produced by these bacteria can lead to toxic reactions. Besides diabetics, victims include premature infants and patients with cirrhosis, cancers, infections of the urinary or gastrointestinal tract, and transplant recipients.

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In the laboratory, the newly produced monoclonal antibody neutralized endotoxin toxicity and prevented death from bacteremia in animals injected with a wide variety of gram-negative bacteria.

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National Heart, Lung, and Blood Institute

The National Heart, Lung, and Blood Institute (NHLBI) maintains extensive research interest in diabetes as it is a known risk factor for cardiovascular diseases. An estimated 25 percent of all diabetics have some form of cardiovascular disease.

Diabetics frequently are found to have an increased level of triglycerides and other blood lipids, which may contribute to the increased level of heart attacks and atherosclerosis among them. Finding a way to reduce the level of these blood lipids could reduce the incidence of cardiovascular diseases among diabetics.

NHLBI grantee Dr. William Connor at the Oregon Health Science University in Portland has been studying the effects of various diets on blood lipid levels. He and his coworkers have found that one way to lower cholesterol and triglycerides is to eat a diet high in fish oils. In a study of 20 patients with elevated levels of triglycerides and cholesterol, those fed a diet high in the certain fatty acids found in fish oil had a much greater decrease in blood triglycerides than those fed a low-fat diet or a diet high in vegetable oils while all groups had similar decreases in blood cholesterol levels. Some patients consuming the fish oil diet experienced as much as a 79 percent reduction in blood triglycerides compared with individuals on the vegetable oil diet. The investigators concluded that a high intake of fish oils may be useful in diets to lower elevated blood lipids, a major risk factor for coronary heart disease.

NHLBI grantees at the University of Texas Health Sciences Center in San Antonio are studying diabetes and cardiovascular risk in Mexican-Americans. Dr. Michael Stern and his colleagues have formulated a new perspective on impaired glucose tolerance and its relation to cardiovascular disease. Impaired glucose tolerance (IGT) has been considered a transitional state between normalcy and diabetes. The researchers think that IGT in some populations may instead represent one of three different states.

The evidence for this interpretation lies in the bimodal distribution of glucose tolerance within certain populations. In this case, bimodality means that testing large numbers of a given population will result in a curve that shows two distinct peaks for impaired glucose tolerance: one peak clearly within the "normal" range and another, smaller one clearly elevated. The populations that demonstrate bimodality--those that are of New World or Pacific Island origin--also have a higher incidence of diabetes.

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Dr. Stern theorizes that because of the double-peak distribution, IGT may mean one of three things: an individual normally has a high level of glucose and is not diabetic, is diabetic but appears to test within the high values of normal, or is indeed in transition from normalcy to a diabetic state. It is not possible to discriminate among the three states by the standard glucose tolerance test.

This finding suggests that physicians should recognize IGT not as a single entity but as any of several states, especially among certain populations. Repeat glucose tolerance tests should be performed to determine whether the patient is progressing to diabetes or has reached a static level of high plasma glucose. Still, the traditional clinical advice to maintain ideal weight, exercise, stop smoking, and decrease the amount of saturated fat and cholesterol in the diet appears to be sound, especially since these recommendations promote overall good health. It remains for a marker to be discovered that will indicate the prediabetic state more certainly than IGT.

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National Institute of Dental Research

The National Institute of Dental Research (NIDR) supports research on the dental complications of diabetes because persons with diabetes are particularly susceptible to peridontal diseases, oral fungal infections, reduced salivation, and diminished senses of taste and smell.

The nature of the relationship between periodontal diseases and diabetes, however, is not yet clear. NIDR-supported dental scientists from the State University of New York (SUNY) at Buffalo in collaboration with NIADDK-sponsored scientists have teamed with diabetes experts in Phoenix, Arizona, to study the Pima Indians--a native American tribe with the highest rate of diabetes in the world.

Their findings show that markedly severe periodontal diseases are common complications of NIDDM. This team also found that periodontal diseases develop at an earlier age in Pima Indian diabetics than in nondiabetics and appear to be associated with B. gingivalis, an organism suspected of causing gum disorders. One-third of the diabetic Pima Indians had lost all of their teeth; less than 2 percent of nondiabetic Pimas showed similar tooth loss. The researchers also suggested that the presence of periodontal diseases in a diabetic can complicate the management of the medical problem because bacterial infection and inflammation in the gums can interfere with the regulation of blood sugar levels.

Future studies will focus on a broader understanding of the cause of periodontal diseases, on better approaches to treatment, and on the ultimate prevention of this serious complication of diabetes.

NIDR intramural scientists continue to study the basic causes of juvenile-onset diabetes. Under the direction of Dr. Abner L. Notkins, the scientists are examining the roles of viruses and immunity in human and animal models of diabetes. They believe that some cases of diabetes involve an immunological "mistake" in which the body produces antibodies, disease-fighting proteins, against itself. Normally, immune responses destroy invading bacteria, viruses, and tumors. When misdirected, however, they can destroy the patient's own tissues. Many patients with juvenile diabetes have autoantibodies in their blood, and researchers believe that these autoantibodies can attack islet cells and possibly produce diabetes.

More recently, Dr. Notkins and his colleagues have detected these autoantibodies in healthy siblings of diabetic children from 2 to 74 months before the onset of diabetes. This is a major step in identifying persons at high risk of developing this disorder.

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Diabetes patients often exhibit both thickening of the membrane just below the skin (basement membrane) and disturbances in bone formation. Intramural investigators at NIDR are currently using sophisticated monoclonal antibody and recombinant DNA techniques in efforts to understand the nature of these changes. Studies are also being conducted to test the use of antidepressants to relieve the chronic pain from nerve damage (neuropathy) associated with diabetes. Other investigators are working to characterize the specific types of sensory loss seen in diabetic patients.

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National Institute of Neurological and
Communicative Disorders and Stroke

The National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) is the focal point within the Federal Government for research on diabetic neuropathy, a serious neurological complication affecting nearly 10 percent of the more than 10 million diabetics in the United States. Symptoms of diabetic neuropathy may include burning sensations, numbness, weakness, and paralysis in the hands and feet. Some scientists think these symptoms are caused by the effect of diabetes on metabolism within nerve cells. There is mounting evidence, however, that symptoms may be the indirect result of blood vessel damage caused by diabetes. Other scientists believe diabetic neuropathy cannot be explained by any single mechanism.

Studies by NINCDS grantee Dr. Peter Dyck and colleagues at the Mayo Clinic in Rochester, Minnesota, support the damaged blood vessel theory. This year, the research team found that diabetic rats supplied with increased oxygen were slow to develop the abnormal nerve conduction characteristic of diabetic neuropathy. Furthermore, nondiabetic rats exposed to long periods of decreased oxygen developed nerve conduction abnormalities typically seen in diabetic rats. Since low oxygen levels result from decreased blood flow, this research supports the team's earlier finding that constricted blood vessels are a component of diabetic neuropathy in humans.

These researchers have now begun an epidemiological study of the prevalence of neurological complications of diabetes. They devised a computerized profile of neurological symptoms to standardize the criteria for determining disability due to such complications. One goal of this research is to identify similarities among patients afflicted with diabetes complications.

Unexpected information about diabetics has emerged from studies at the NINCDS-supported Clinical Smell and Taste Research Center at the University of Pennsylvania in Philadelphia. Drs. James Snow and Gregg Settle and their colleagues found that, in a taste test, diabetics and their nondiabetic relatives recognized the taste of the glucose less readily than they did the sugar fructose. In contrast, glucose recognition was significantly stronger than fructose recognition in people who had no diabetes and no family history of the disease. These results suggest that a general lack of glucose recognition may underlie NIDDM. The data also suggest that glucose may have a taste recognition mechanism distinct from that of fructose and other sugars.

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At the Michael Reese Hospital and Medical Center in Chicago, Illinois, NINCDS grantee Dr. Dale Pelligrino is studying the role of insulin in regulating brain metabolism. In studies of experimentally induced diabetes in goats, Dr. Pelligrino discovered that this animal's metabolic responses differed from those of dogs and humans. These findings rule out goats, and probably other cud-chewing animals, as models for diabetes studies.

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National Institute of Child Health and Human Development

A very high incidence of congenital malformations occurs in infants born to women with diabetes mellitus, and the frequency of these malformations has risen. They are now the leading cause of perinatal mortality in the diabetic pregnancy. The wide variety of diabetes-induced abnormalities includes heart, neural tube, vertebral, and limb malformations. Macrosomia (overly high birth weight), late intrauterine death, and respiratory distress syndrome are also significant problems among diabetic pregnancies. In addition, pregnancy itself sometimes prompts in the mother development of either a temporary metabolic disturbance, known as gestational diabetes mellitus, or long-term diabetes. The National Institute of Child Health and Human Development (NICHD) supports four Perinatal Emphasis Research Centers in the area of diabetes.

By electronically monitoring fetal heart rate and movement, researchers have been able to examine fetal cycles. Active and quiet periods lengthen with age in normal fetuses. This is not the case with the fetuses of insulin-controlled diabetics, suggesting a delay in maturation.

Several groups of investigators supported by NICHD contracts and grants are examining the mechanisms by which diabetes interferes with normal fetal growth. Hyperglycemia (too much glucose in the blood), excessive amounts of chemical compounds known as ketones, and the presence of hormones inhibiting the production of the growth-mediating hormone somatomedin have all been shown to independently interfere with normal development. Using culture techniques, researchers are studying the effects of these factors on rat and mouse embryos. Defining the biochemical alterations produced will provide a better understanding of how maternal diabetes produces birth defects.

Home monitoring of glucose levels by pregnant diabetics is being analyzed in relation to the frequency of poor pregnancy outcome in a study of more than 900 women. The Diabetes in Early Pregnancy Project is the first large-scale study to enroll women before or immediately after conception and to examine the risks of fetal loss and congenital malformations prospectively. Early enrollment is particularly important because most fetal malformations are determined in the first 6 weeks after conception. When their pregnancy was confirmed, the diabetic women had a health assessment and began daily home monitoring of their glucose levels. Blood was analyzed weekly. Preliminary data show that spontaneous abortions are not more common among these well-controlled diabetics than among control women. Comparisons of malformations in pregnancies that went to term are now being analyzed. Five medical centers are participating in this project, which is being coordinated by Dr. James Mills, an NICHD intramural scientist.

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Grantee Dr. Fredda V. Ginsberg-Fellner and colleagues at the City University of New York have shown that intensive home glucose monitoring affects the birth weight of babies born to diabetic women. Two groups of pregnant diabetics were studied. A control group followed conventional treatment guidelines. The other group performed both fasting and after-meal glucose monitoring so that a need for insulin could be identified quickly. It was found that macrosomia was four times more common among babies born to women in the control group.

NICHD is also involved in applying computer technology to help diabetics monitor themselves. Dr. David Rodbard, NICHD intramural scientist, has developed a number of innovative programs that can be used on home computers. Graphs and statistical displays are accompanied by detailed written descriptions that give reasons for suggested changes in diet or in insulin dosage, timing, or type. The patient is also advised when to call the physician. Customized treatment plans can be computed, and a patient's glucose profile can be analyzed in terms of daily or weekly changes. The programs are now being evaluated in controlled clinical trials at medical centers throughout the Nation, with special emphasis on their use for children, adolescents, and pregnant women.

The relationship between the use of oral contraceptives and diabetes is also under study. As part of an NICHD contract headed by Dr. Thomas B. Clarkson at Wake Forest University in Winston-Salem, North Carolina, oral glucose tolerance tests and insulin assays are being administered to oral contraceptive users, who are classified as short-, intermediate-, or long-term users of either high- or low-dose preparations. A sample of women are being given intravenous glucose tolerance tests to determine whether impaired glucose tolerance in oral contraceptive users results from insulin resistance or impaired production of insulin. A second contract study will be undertaken to corroborate the results from the first. Comparisons of users of all oral contraceptive compounds will be provided through one of the world's largest metabolic data bases, located in England. Because of its size and prospective design, the English study should clearly identify time and dosage trends in metabolism. These studies will provide information on precisely how contraceptive steroids alter metabolism, contributing to an understanding of their diabetes-inducing potential.

Other research is aimed toward discovering a marker that can be used to indicate latent IDDM among the general population. The presence of islet cell autoantibodies (antibodies that are directed against the body's own cells) has been suggested as such a marker. In a study of school children, grantee Dr. Noel K. MacLaren and colleagues at the University of Florida at Gainesville found that such antibodies are indeed found only among children who are genetically susceptible to IDDM.

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National Institute of Child Health and Human Development

A very high incidence of congenital malformations occurs in infants born to women with diabetes mellitus, and the frequency of these malformations has risen. They are now the leading cause of perinatal mortality in the diabetic pregnancy. The wide variety of diabetes-induced abnormalities includes heart, neural tube, vertebral, and limb malformations. Macrosomia (overly high birth weight), late intrauterine death, and respiratory distress syndrome are also significant problems among diabetic pregnancies. In addition, pregnancy itself sometimes prompts in the mother development of either a temporary metabolic disturbance, known as gestational diabetes mellitus, or long-term diabetes. The National Institute of Child Health and Human Development (NICHD) supports four Perinatal Emphasis Research Centers in the area of diabetes.

By electronically monitoring fetal heart rate and movement, researchers have been able to examine fetal cycles. Active and quiet periods lengthen with age in normal fetuses. This is not the case with the fetuses of insulin-controlled diabetics, suggesting a delay in maturation.

Several groups of investigators supported by NICHD contracts and grants are examining the mechanisms by which diabetes interferes with normal fetal growth. Hyperglycemia (too much glucose in the blood), excessive amounts of chemical compounds known as ketones, and the presence of hormones inhibiting the production of the growth-mediating hormone somatomedin have all been shown to independently interfere with normal development. Using culture techniques, researchers are studying the effects of these factors on rat and mouse embryos. Defining the biochemical alterations produced will provide a better understanding of how maternal diabetes produces birth defects.

Home monitoring of glucose levels by pregnant diabetics is being analyzed in relation to the frequency of poor pregnancy outcome in a study of more than 900 women. The Diabetes in Early Pregnancy Project is the first large-scale study to enroll women before or immediately after conception and to examine the risks of fetal loss and congenital malformations prospectively. Early enrollment is particularly important because most fetal malformations are determined in the first 6 weeks after conception. When their pregnancy was confirmed, the diabetic women had a health assessment and began daily home monitoring of their glucose levels. Blood was analyzed weekly. Preliminary data show that spontaneous abortions are not more common among these well-controlled diabetics than among control women. Comparisons of malformations in pregnancies that went to term are now being analyzed. Five medical centers are participating in this project, which is being coordinated by Dr. James Mills, an NICHD intramural scientist.

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Grantee Dr. Fredda V. Ginsberg-Fellner and colleagues at the City University of New York have shown that intensive home glucose monitoring affects the birth weight of babies born to diabetic women. Two groups of pregnant diabetics were studied. A control group followed conventional treatment guidelines. The other group performed both fasting and after-meal glucose monitoring so that a need for insulin could be identified quickly. It was found that macrosomia was four times more common among babies born to women in the control group.

NICHD is also involved in applying computer technology to help diabetics monitor themselves. Dr. David Rodbard, NICHD intramural scientist, has developed a number of innovative programs that can be used on home computers. Graphs and statistical displays are accompanied by detailed written descriptions that give reasons for suggested changes in diet or in insulin dosage, timing, or type. The patient is also advised when to call the physician. Customized treatment plans can be computed, and a patient's glucose profile can be analyzed in terms of daily or weekly changes. The programs are now being evaluated in controlled clinical trials at medical centers throughout the Nation, with special emphasis on their use for children, adolescents, and pregnant women.

The relationship between the use of oral contraceptives and diabetes is also under study. As part of an NICHD contract headed by Dr. Thomas B. Clarkson at Wake Forest University in Winston-Salem, North Carolina, oral glucose tolerance tests and insulin assays are being administered to oral contraceptive users, who are classified as short-, intermediate-, or long-term users of either high- or low-dose preparations. A sample of women are being given intravenous glucose tolerance tests to determine whether impaired glucose tolerance in oral contraceptive users results from insulin resistance or impaired production of insulin. A second contract study will be undertaken to corroborate the results from the first. Comparisons of users of all oral contraceptive compounds will be provided through one of the world's largest metabolic data bases, located in England. Because of its size and prospective design, the English study should clearly identify time and dosage trends in metabolism. These studies will provide information on precisely how contraceptive steroids alter metabolism, contributing to an understanding of their diabetes-inducing potential.

Other research is aimed toward discovering a marker that can be used to indicate latent IDDM among the general population. The presence of islet cell autoantibodies (antibodies that are directed against the body's own cells) has been suggested as such a marker. In a study of school children, grantee Dr. Noel K. MacLaren and colleagues at the University of Florida at Gainesville found that such antibodies are indeed found only among children who are genetically susceptible to IDDM.

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Dr. Ginsberg-Fellner at the City University of New York is also studying the presence of antibodies against insulin in the blood of children who are developing IDDM. Blood is tested when the diabetes is diagnosed as well as during the development of the disease. It has been determined that these antibodies are present at the onset of diabetes in most of the children. The researchers suggest that insulin may be released in a form that stimulates the immune system to attack it just before the onset of symptoms of diabetes. Similar findings were noted by grantee Dr. Lori Laffel at the Children's Hospital in Boston, Massachusetts, in her study of antibodies against insulin and insulin receptors among diabetics, prediabetics, and patients with insulin allergy.

The pancreatic islet cells of insulin-dependent diabetics malfunction, and transplantation of normally functioning islets has been suggested as a possible treatment. Grantee Dr. Alyne Ricker, also at Boston Children's Hospital, is working to protect transplanted insulin-secreting tissues from host defenses by microencapsulating the transplanted cells. This technique has effectively reduced hyperglycemia in diabetic mice grafted with insulin-secreting cells.

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National Eye Institute

Diabetes is responsible for loss of vision in thousands of Americans each year. In fact, it is the leading cause of new cases of blindness in people 20 to 74 years old.

Over a period of years, diabetes causes a series of harmful changes in the retina, the delicate light-sensing tissue lining the inside of the eye. The resulting visual loss may be profound, as it often is when diabetic retinopathy progresses to the point where hemorrhaging prevents incoming light from reaching the retina. Or, the visual deficit may be much less severe, as in diabetic macular edema when excess fluid swells retinal tissue, blurring vision. But even this milder degree of impairment can dramatically affect the quality of life for the diabetic person whose visual acuity has declined just enough to prohibit reading or driving a car.

The National Eye Institute (NEI) supports research aimed at overcoming the full spectrum of diabetes-induced ocular problems, which are believed to affect as many as 40 percent of our Nation's 10 to 11 million diabetics.

In one NEI-supported clinical trial, the Early Treatment Diabetic Retinopathy Study (ETDRS), laser treatment is being evaluated in patients who are mildly affected, i.e., still in the early stages of diabetic eye disease. Recent results from this study show that it is possible to halt or even reverse the mild to moderate reduction in visual acuity that afflicts many people with diabetic macular edema.

At the beginning of the study, eyes with macular edema were randomly assigned to receive either immediate or deferred treatment. Eyes in the immediate treatment group underwent focal photocoagulation with the argon laser. The objective of this technique is to coagulate only the tissue suspected of leaking fluid into the macula, thereby causing retinal swelling. The technique differs from the more extensive laser treatment employed in the previously reported Diabetic Retinopathy Study (DRS). In the DRS, panretinal photocoagulation was evaluated in people with advanced diabetic retinopathy. It was found to be effective in preventing severe visual loss and blindness caused by abnormal development of retinal blood vessels.

In the ETDRS, a total of 1,490 eyes were assigned to the deferred treatment group while 754 received immediate focal photocoagulation. At 3 years, 24 percent of eyes in the untreated group had lost a significant amount of visual acuity, whereas only 12 percent of those in the treated group had done so. Focal treatment also increased the chance of visual improvement, decreased the frequency of persistent macular edema, and caused only minor visual field losses. The beneficial effects of treatment led the ETDRS investigators to recommend that all eyes with significant macular edema be considered for focal photocoagulation.

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These recent findings from the ETDRS will result in a substantial increase in the number of diabetics who are eligible for some type of laser treatment to preserve their eyesight and who require regular eye examinations to find out if treatment is indicated. This means primary care physicians will have to play a more active role in referring their diabetic patients to specialists trained to diagnose and treat diabetic eye disease. For not only do we know how to prevent severe visual loss associated with advanced proliferative retinopathy, we now know how to combat the milder though still disturbing effects of diabetic macular edema.

There was good news this year also for diabetics who have experienced one of the most devastating events in the progression of diabetic retinopathy--a severe vitreous hemorrhage. This occurs when abnormal new blood vessels growing from the retina rupture and bleed into the vitreous. When the vitreous, normally a clear gel that fills the center of the eyeball, becomes clouded with blood, vision is obscured. In addition, scar tissue may form and cause detachment of the retina. Again, permanent visual loss, even total blindness, may result.

In the NEI-supported Diabetic Retinopathy Vitrectomy Study (DRVS), two approaches to surgical restoration of sight were compared in people who had suffered a vitreous hemorrhage causing serious loss of vision. The surgery, called vitrectomy, involves removal of the blood and scar tissue from the center of the eye. Early vitrectomy was compared to deferred vitrectomy to find out if better visual results can be achieved by operating soon after the hemorrhage has occurred or by waiting a year in hopes that the hemorrhage will clear on its own.

In the DRVS, 616 eyes with a hemorrhage that had caused a dramatic reduction in visual acuity for at least a month were randomly assigned to one of the two treatment groups. At the 2-year followup examination, the investigators found that 24.5 percent of eyes that underwent early vitrectomy had a visual acuity of 20/40 (driving vision in most states), while only 15.2 percent of those in the deferred treatment group had achieved such acuity. The beneficial effect of early treatment was more apparent in those patients who had type I (juvenile-onset) diabetes. In these eyes, 36 percent of the early vitrectomy group, compared to 12 percent in the deferred vitrectomy group, had a visual acuity of 20/40 or better after 2 years. The investigators concluded that early vitrectomy can improve chances of long-term recovery of good vision in some eyes.

The NEI is concerned not only with appropriate management of diabetic eye disease once it develops, but also with its prevention. In one ongoing multicenter study involving 600 insulin-dependent diabetics, a new drug is being evaluated to determine whether it can protect the retina from diabetes-induced damage. The NEI is sponsoring the Sorbinil

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Retinopathy Trial in collaboration with Pfizer, Inc., the pharmaceutical firm that developed the drug being tested. Half of the patients will receive the drug sorbinil and half a placebo to determine if the drug can prevent or slow down the development of diabetic retinopathy in people who are known to be at high risk for this disorder but do not yet show serious signs of eye disease. During the past year, efforts to recruit patients were expanded and the number of patients enrolled increased dramatically.

The NEI also supports a wide range of research projects conducted by basic scientists and clinical investigators dedicated to fighting the ocular complications of diabetes. Thanks to their efforts and the efforts of researchers participating in NEI-supported multicenter clinical trials described above, millions of Americans with diabetes will be able to avoid many of the ocular complications of this disease and enjoy good vision throughout their lives.

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National Institute of Environmental Health Sciences

Dr. Brooke Mossman, a National Institute of Environmental Health Sciences (NIEHS) grantee, and her colleagues at the University of Vermont College of Medicine in Burlington are studying how n-nitroso compounds, a broad class of chemicals that are ubiquitous in the environment, damage insulin-producing cells. Among these compounds for example is Vacor®, a rodenticide known to cause diabetes in man. In recent studies, these researchers have examined whether cell damage induced by two n-nitroso compounds, streptozotocin (SZ) and chlorozotocin (CLZ), involves oxygen-free radicals, extremely reactive groups of atoms. To address this question, they evaluated compounds that are scavengers of oxygen-free radicals. These scavenger compounds were tested for their ability to prevent SZ- or CLZ-induced damage to insulin-producing cells in the laboratory. The data indicated that a dual mechanism involving both the generation of certain radicals and the activation of a particular biochemical pathway, the poly(ADP ribose) system, may promote SZ-induced toxity of insulin-producing cells. Injury to insulin-producing cells by CLZ, on the other hand, could not be prevented by any of the free radical scavengers tested or by inhibitors of the enzyme that activates the poly(ADP ribose) pathway. Specialized blood cells are now being studied as a possible intermediary cell in this disease. Dr. Mossman and her colleagues are also looking at whether the insulin-producing cells are capable of repairing themselves after interaction with diabetogenic chemicals. The investigators have examined the interaction of SZ and CLZ with the DNA of insulin-producing cells using a sensitive technique to determine DNA damage. Both CLZ and SZ have been found to cause significant but different types of damage to DNA. Further experiments are planned to determine whether this damage is "repaired" with time in pancreatic cell tumors, in normal pancreatic beta cells, and in connective tissue cells, of fibroblasts. The results to date from comparative studies with fibroblasts suggest that the beta cell's repair capacity is minimal.

Finally, this team of investigators has collected data suggesting that the association between the n-nitroso moiety and a particular carbon atom of glucose is important in eliciting cell injury. By modifying the structure of or removing the glucose in n-nitroso compounds, diabetogenicity is prevented.

Grantee Dr. Glenn L. Wilson and colleagues at the University of South Alabama College of Medicine in Mobile have been using tissue culture techniques to study chemicals that cause diabetes. The investigators have examined how radical scavengers influence the effects of the insulin-producing cell toxin, alloxan. It was found that two scavengers reduced the toxic effects of alloxan. In

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addition, inhibitors of the enzyme that activates the biochemical pathway implicated in SZ-induced toxicity effectively reduced alloxan-induced beta cell toxicity. The investigators believe that the initial step in SZ-induced insulin-producing cell toxicity is the particular modification of DNA bases leading to DNA damage. However, no studies have quantitatively evaluated the extent of DNA damage in insulin-producing cells and correlated this damage with toxicity. Therefore, these two parameters were compared following exposure of rat insulin-producing cell cultures to SZ or another n-nitroso compound, n-methyl-n-nitrosourea (MNU). Although SZ was 10 times more toxic than MNU with respect to insulin production, both compounds had similar effects on DNA. These data indicate that it is not simply the damage to the DNA that leads to the toxicity of SZ, since MNU causes comparable DNA damage at a nontoxic concentration (i.e., no effect on insulin release).

One consequence of diabetes is a change in the way the liver metabolizes environmental compounds. Grantee Dr. David Cook and his associates at the University of Nebraska Medical Center in Omaha have begun a new study relating this altered metabolism in the liver to the reaction of diabetics to toxic environmental chemical exposure. An understanding of these relationships is important to those who oversee the care of diabetic patients and to those interested in the hormonal regulation of biochemical processes. Since certain specialized proteins are important in such processes, these investigators are developing antibodies monospecific to these normal and diabetic proteins found in the liver, which may appear in diabetes mellitus. Characterization of this enzyme may clarify the mechanism that causes an other than normal metabolism of drugs in the livers of diabetics.

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National Institute on Aging

One of the most frequently occurring disorders associated with old age is diabetes mellitus. Scientists do not fully understand all the biochemical and physiological changes that contribute to the development of diabetes, and it is sometimes difficult to distinguish these changes from those occurring normally with age such as decreased glucose tolerance. The National Institute on Aging (NIA) supports research to determine the underlying mechanisms involved in diabetes, to develop improved methods of diagnosis and treatment, and to investigate the behavioral and psychosocial impact of diabetes on elderly patients and their families.

Noninsulin-dependent diabetes (NIDDM) is the more common form of the disease in older adults. Many investigators have attempted to resolve two fundamental questions about NIDDM: Does it represent a defect in insulin production, insulin release, or insulin action at the cellular level, or is it the result of phenomena that occurs as part of the aging process?

NIA grantee Dr. Byron Hoogwerf and his colleagues at the University of Minnesota in Minneapolis are studying age-related changes in pancreatic beta cells as a means of providing insight into diabetes mellitus in older adults. The researchers are using a simple noninvasive test to determine insulin production in humans. C-peptide is a compound secreted from beta cells in direct proportion to insulin secreted from beta cells. It was previously shown that insulin production can be determined by measuring the excretion of C-peptide in the urine.

By evaluating C-peptide levels in both diabetic and nondiabetic individuals under a variety of dietary conditions, Dr. Hoogwerf has shown that there seems to be an increase in C-peptide production, and therefore insulin production, with increasing age. Nevertheless, in some older subjects this response is insufficient to keep the response to glucose in the range of that seen in younger subjects.

In another NIA-supported study on diabetes mellitus, biochemist Dr. Charles Howard and colleagues at the Oregon Regional Primate Research Center in Beaverton, Oregon, have been working with a species of monkey (Macaca nigra) that is a particularly good research model because over 70 percent of them will develop diabetes spontaneously as they age. Thus, researchers need not use experimental methods to induce diabetes but can study the natural development of the disease in a species closely related to humans. By studying these monkeys over their normal lifespan, investigators can monitor the early stages of diabetes, with the goal of uncovering possible interventions.

Antibodies to pancreatic islet cells (ICA) have been identified in the blood of aging prediabetic and diabetic M. nigra in association with islet cell degeneration. The

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presence of ICA was found to be correlated with both metabolic status and morphological changes in the islet cells. Eighty-seven percent of nondiabetic monkeys were ICA-negative; more than 90 percent of monkeys with mild to severe hormonal or glycemic (glucose) abnormalities were ICA-positive. More than 80 percent of the monkeys with any evidence of islet cell deterioration from samples examined at the time of autopsy or biopsy were also ICA-positive. From these findings, Dr. Howard has concluded that the presence of ICA in the blood strongly indicates the presence of islet cell lesions, and the loss of cells due to these lesions can cause further carbohydrate impairment.

In general, IDDM in humans is associated with beta cell necrosis while NIDDM involves defects in insulin secretion or resistance to insulin action. However, many maturity-onset cases do not fit this simple categorization. Although ICA's have been found in patients with NIDDM, islet cell degeneration has not been an accepted characteristic of this type of diabetes. Using data from M. nigra, along with data from other relevant studies, it may be possible to explain this discrepancy, delineate a major form of maturity-onset diabetes, and improve therapy.

The potential significance of Dr. Howard's work is that, by using a simple blood test, physicians may be able to identify a subpopulation of individuals with NIDDM. Treatment initiated in the very early stages of the disease may help prevent further cell damage.

Cell culture studies are also important in research on diabetes. To date, only a few normal cells have been successfully cultured as models for studies of aging. Scientists have been able to culture abnormal (that is, cancer) cells, but such cells do not allow investigations into the normal changes that occur with aging. Now, Drs. Lu Zhongding and Robert Gregerman and colleagues at the NIA's Gerontology Research Center (GRC) in Baltimore, Maryland, have succeeded in culturing normal mature fat cells (adipocytes).

Scientists had previously assumed that mature fat cells would not divide under laboratory conditions. But after success in culturing preadipocytes (precursors of fat cells), the GRC investigators succeeded in isolating and then growing mature fat cells. They are using these cells to determine whether the age of the donor animal programs the adipocytes to exhibit in cell culture the same type of biochemical change that occurs in the living animal. This work may provide scientists with a new cell type that will enable them to study measurable biological and molecular events. This, in turn, may help researchers determine how and why age-related changes such as glucose intolerance occur. For example, cellular changes in fat cells may be the result of genetic programming or, on the other hand, the secondary consequences of environmental conditions.

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Division of Research Resources

Significant strides toward achieving the promise that pancreas transplantation holds as a treatment for the thousands of diabetics who are likely to develop blindness or other devastating complications of their disease have been made by Dr. David Sutherland and colleagues at the University of Minnesota General Clinical Research Center (GCRC) in Minneapolis. The University of Minnesota GCRC is one of more than 72 such centers studying diabetes.

Nearly a third (32 patients) of the 103 patients who have received pancreas transplants since 1978 have shown signs of long-term engraftment and no longer require insulin, including 18 who have been insulin independent for more than 1 year. During 1985 the success rate increased to 64 percent, with engraftment occurring in 14 of 22 diabetics who underwent transplantation. Moreover, Dr. Sutherland and his team have documented regression of kidney disease in four transplant recipients who have been insulin independent for more than 1 year.

These developments brighten the prospects for diabetics who cannot achieve reasonable control of their blood sugar levels with the standard regimen of insulin injections, dietary management, and exercise. High blood sugar levels--perhaps in combination with other factors--progressively damage the blood vessels and nerves, causing heart and kidney failure, blindness, and other complications.

Among the many complications that can afflict diabetics is rheumatic hand syndrome, which can transform simple tasks into ordeals. Progressive stiffness and loss of sensation in the hands may prevent affected diabetics from performing job-related duties, jeopardizing their livelihood. At the University of New Mexico GCRC in Albuquerque, researchers led by Dr. R. Philip Eaton administered the new drug sorbinil to three diabetics with rheumatic hand condition.

After a month of sorbinil therapy, all three patients were able to hold and use their insulin syringe, a task that had been impossible for them before treatment. Continued treatment allowed one patient to resume performing all of her duties as a nurse, from measuring blood pressure to administering medication. All three patients regained the ability to write, and one reported being able to tie flies to a fishing line. In followup studies of two patients, the researchers found that sorbinil therapy also improved nerve conductivity and restored sensation in their hands.

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Sorbinil inhibits the activity of an enzyme that participates in the synthesis of sugar alcohols. By interrupting this biochemical pathway, Dr. Eaton speculates, the drug may prevent the abnormal accumulation of alcohols and the consequent swelling of connective tissue, which is suspected of causing joint stiffness.

In addition to medication and diet, exercise is a fundamental component of therapy for diabetics. A mix of continuous and intermittent exercise, the kind typical of such childhood games as tag and soccer, reduce blood sugar levels in insulin-dependent diabetic children, according to the first phase of research being conducted by DRR grantee Dr. Irene N. Sills in New York at the Children's Hospital of Buffalo.

The finding, based on a study of five boys with IDDM, is a first step toward filling the large void in information about how exercise affects young diabetics. Dr. Sills notes that exercise often is recommended to improve glucose tolerance in IDDM patients. These recommendations, however, are based on studies of diabetic adults who engaged in continuous forms of exercise such as running, bicycling, and swimming.

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OUTLOOK

As the Institute reports illustrate, research on diabetes is advancing on many interrelated fronts. While each Institute supports research that ostensibly deals with that Institute's own health territory, for example, the eye or cancer, no one can predict all the fields that a given research advance may affect. One reason for this is that diseases like diabetes affect many different systems and organs. More important, basic biomedical investigation, an emphasis of all the National Institutes of Health, provides an understanding of how living organisms function in normal and disease states. Without this context of understanding to point the way to possible new treatment approaches, clinical research would be a hit-or-miss process. Without the methods developed in basic, often undirected, research, investigation of specific defects such as those associated with diabetes would be much slower, if not impossible.

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